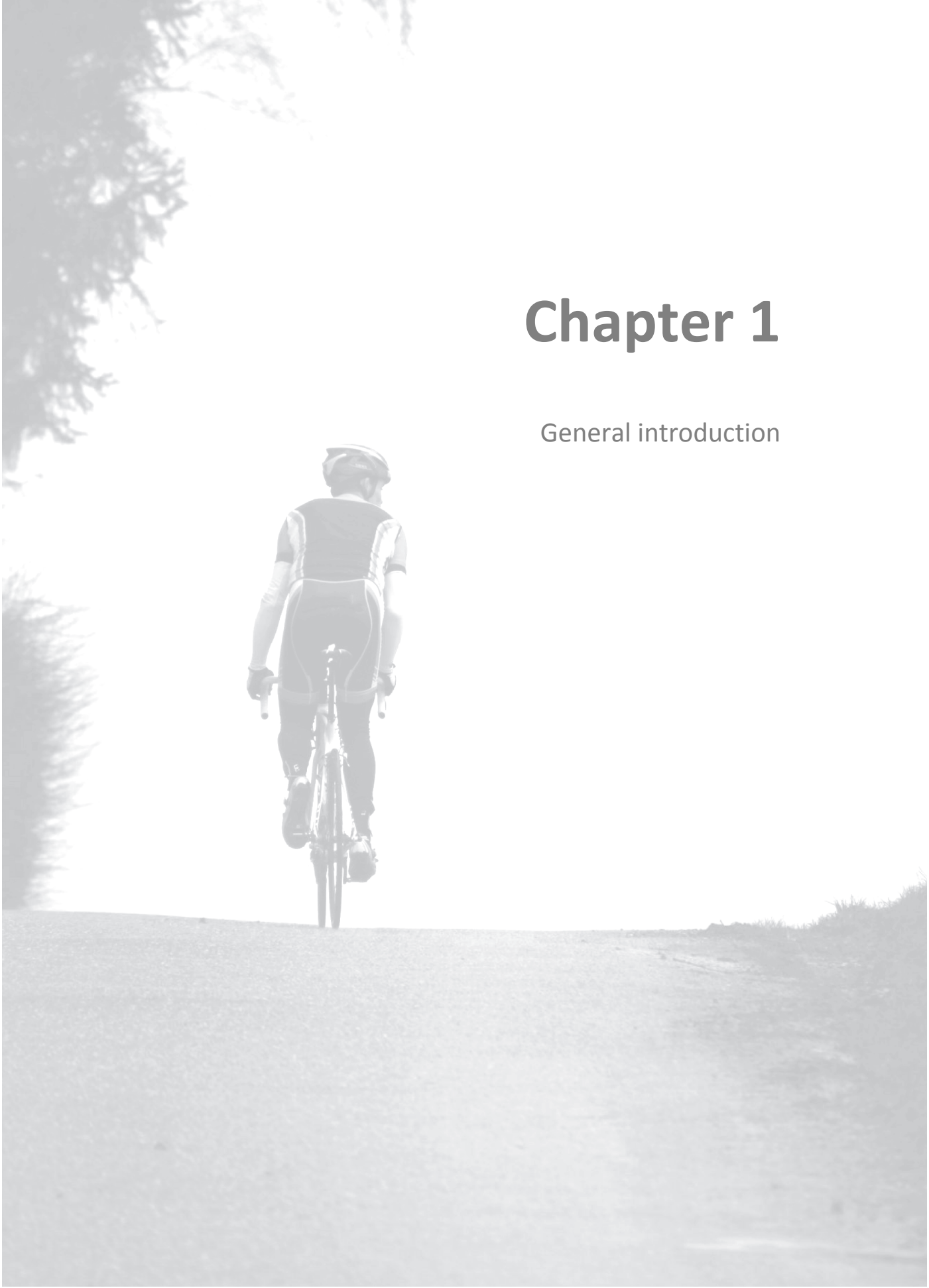

Chapter 1

General introduction

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown cause, characterized by the formation of noncaseating epithelioid cell granulomas, consisting of mononuclear phago- and lymphocytes, in various organ systems.[1-3] The diagnosis sarcoidosis is established according to the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guideline by excluding other granulomas provoking disorders supported by a compatible clinicoradiologic presentation together with histological evidence of granulomas (Figure 1.1).[1,4] However, in patients presenting with Löfgren's syndrome, characterized by fever, erythema nodosum, bilateral hilar adenopathy, and polyarthralgias, a biopsy will not be necessary to establish the disease because of the specific disease presentation.[5] Generally, chest radiographs are graded according to the radiographic staging proposed by DeRemee: stage 0 (no visible intrathoracic abnormalities), stage I (bilateral hilar lymphadenopathy), stage II (bilateral hilar lymphadenopathy and parenchymal infiltration), stage III (parenchymal infiltration without bilateral hilar lymphadenopathy), and stage IV (advanced lung fibrosis).[1,6]

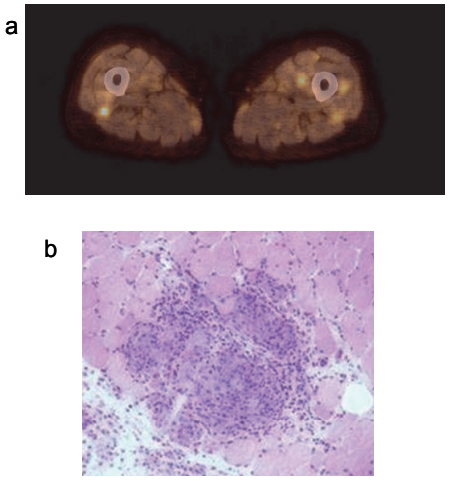

Figure 1.1 **a.** PET/CT image of a sarcoidosis patient showing multiple foci with increased fluorodeoxy-glucose (FDG) uptake in the muscles of the lower extremities. **b.** Noncaseating granuloma present in a biopsy obtained from the left quadriceps muscle of a patient with sarcoidosis.

Epidemiology

The disease occurs throughout the world, affecting both men and women of all races and ages.[1] However, sarcoidosis shows a predilection for young adults in their working age (25-45 years).[2] In general, the disease is more severe in black compared to white patients.[7] African-Americans also had about a three-fold higher age-adjusted annual incidence rate (35.5 cases per 100,000) compared with Caucasians (10.9 per 100,000).[8] The incidence in the Netherlands is thought to be 20 per 100,000 and the prevalence 50 per 100,000.[9] Scandinavian countries showed the highest prevalence rates.[1,10]

Etiology

Although the etiology of sarcoidosis is still unknown, it is assumed that sarcoidosis is the result of an exaggerated granulomatous reaction after exposure of genetically predisposed persons to specific environmental and occupational agents, such as viruses, metal dusts, insecticides and moldy environments.[1,2,4]

For example, after the World Trade Center disaster, the incidence of sarcoidosis among rescue workers of the Fire Department of New York was increased.[11] Even evidence exists that dental material with silicates might be a factor in the onset of sarcoidosis in dental surgeons.[12] Sarcoidal granulomas have also been reported in tattoos, since the tattoo pigment is foreign body material.[13]

Clinical presentation

The clinical course of sarcoidosis is unpredictable and clinical manifestations are variable, depending on the specific site and extent of the organ involvement, disease activity of the granulomatous process, duration of the illness and severity. Patients may suffer from a wide spectrum of organ-specific symptoms, since every organ can be involved. Most commonly the lungs are affected in approximately 90% of the sarcoidosis patients, resulting in symptoms such as cough, breathlessness and dyspnea on exertion. Besides the lungs, the skin, eyes, heart, lymphatic, nervous and musculoskeletal system are often involved.[1,14,15] In 50-80% of patients with sarcoidosis asymptomatic sarcoid muscle involvement will be detected by muscle biopsy. Symptomatic muscle involvement is rare.[16] Fluorine18-fluoro-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is a sensitive method to detect inflammatory activity in extrathoracic organs, including muscle involvement (Figure 1.1a).[17,18] Patients also frequently visit their physician with non-specific health complaints, such as pain, arthralgia, cognitive failure[19], anxiety, depressive symptoms[20,21], fatigue[22,23], muscle weakness and exercise intolerance.[24-28] Although physical impairments are common problems in sarcoidosis, the number of studies on

this topic are limited. Muscle atrophy is a substantial problem in sarcoidosis with a prevalence of 25% and is associated with impaired exercise capacity.[29] In a previous study, 50% of the sarcoidosis patients reported reduced exercise capacity and 22% general weakness by completing a questionnaire.[24] Besides muscle atrophy various other causes of physical impairments exist, for example inefficient ventilation, oxygen diffusing impairments, physical inactivity and use of corticosteroids.[30] Studies concerning muscle weakness included small study populations or sarcoidosis patients with specific health complaints. Previous studies reported reduced mean values of exercise capacity and muscle strength in sarcoidosis.[25,28,31,32] However, studies about the prevalence of muscle weakness and exercise intolerance in sarcoidosis are scarce.

Fatigue is a clear hallmark of sarcoidosis patients affecting quality of life (QoL) negatively. The etiology of fatigue is still unknown and is most probably multifactorial. Possible factors involved in the etiology of fatigue in sarcoidosis are inflammatory activity[33], sleep disturbances (obstructive sleep apnea syndrome)[34], psychological disorders (depression, anxiety and stress)[21,35], cognitive failures[19] and side effects of drug use.[22] Small fiber neuropathy (SFN) is common in sarcoidosis and linked to fatigue. Symptoms in SFN, like pain and paraesthesias, may also interfere with physical functions and functioning.[36,37]

However, fatigued patients with physical impairments may reduce their daily physical activities, causing more perceived physical problems. This mechanism is also called the negative vicious circle of physical deconditioning.[25] Therefore, muscle weakness or exercise intolerance may explain fatigue complaints partially. Although the influence of physical functions on fatigue and QoL not has been studied extensively, it is likely that improvement of physical functioning has a positive effect on patients QoL.

Course of the disease

In generally, the acute form of sarcoidosis, i.e. Löfgren's syndrome, has a good prognosis.[9] More than 50% of the patients shows a spontaneous remission within two years of the diagnosis, and within a decade for two-thirds with few or no consequences.[2,5] However, the disease shows a progressive or chronic course in 10-30%.[1] Therefore, sarcoidosis is often classified into acute (<2 years) and chronic (3-5 years) phenotypes.[2,38] A worse prognosis is associated with patient and disease characteristics, like black race, extrapulmonary (neurological and cardiac) involvement, and advanced pulmonary disease.[1,9] The mortality rates in sarcoidosis range from 1-8% also as a result of neurological and cardiac involvement or progressive pulmonary insufficiency, mainly due to pulmonary fibrosis or pulmonary hypertension.[39]

Mostly, sarcoidosis-related symptoms are disabling, especially when they are progressive or chronic, and can have a substantial impact on the patients' daily activities and families resulting in a reduced QoL.[40,41] So far, studies using a longitudinal study design to examine changes in physical functions over time in sarcoidosis are

missing. Therefore, no conclusions can be drawn with regard to the course of these physical impairments. This point is of clinical interest in the management of sarcoidosis, since a physiotherapeutic intervention, for instance a rehabilitation program, could offer added value in patients with persistent physical impairments.

Assessment of physical functions and functioning

The management of sarcoidosis patients suffering from physical impairments, requires clinically useful tools to objectify the severity of these impairments. Commonly used physiological tests in current clinical practice to assess disease activity and severity in sarcoidosis include chest radiography, lung function testing and serological parameters.[1] These parameters are only weakly related with fatigue and do not reliably reflect the patients' QoL.[42,43] So, patients without signs of inflammatory activity may suffer from unexplained disabling symptoms, such as fatigue and dyspnea, resulting in a reduced QoL. Frequently used questionnaires to assess fatigue complaints and QoL in sarcoidosis are the Fatigue Assessment Scale (FAS) and World Health Organization Quality of Life-BREF assessment instrument (WHOQOL-BREF).

In other chronic disorders exercise and/or muscle strength testing appeared to be of additional value in the management of the disease.[44] Therefore, it is important to study the added value of physical testing in sarcoidosis patients with unexplained disabling symptoms, especially when a discrepancy exists between clinical findings and routinely used physiological tests. The six-minute walk test (submaximal functional exercise test) and cardiopulmonary exercise testing (maximal exercise test) are commonly used exercise tests in the management of sarcoidosis.[25,45,46] Peripheral muscle weakness can be assessed using the Biodex System 3 Pro[47], Jamar[48] or a hand-held dynamometer (Figure 1.2).[49]

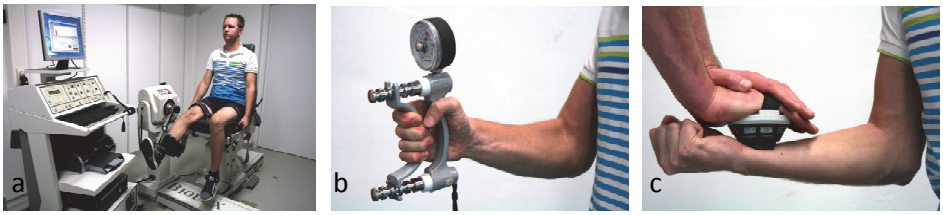

Figure 1.2 Peripheral muscle strength testing in patients with sarcoidosis: **a.** Biodex System 3 pro dynamometer **b.** Jamar dynamometer **c.** Hand-held dynamometer.

Therapeutic options

Pharmaceutical treatment often fails to eradicate persistent fatigue and physical impairments in sarcoidosis.[22] However, exercise training appeared beneficial in improving exercise capacity, dyspnea and QoL and belongs to the standard of care in the treatment of patients with chronic obstructive pulmonary diseases (COPD).[44] Similar improvements were reported in patients with interstitial lung diseases (ild).[50,51] Regrettably, studies reporting about the benefits of exercise training in ild only include ild patients other than sarcoidosis or do not perform a subgroup analysis of the sarcoidosis patients. Obviously, exercise training can fulfil an important role in the treatment of these persistent disabling symptoms. However, studies to support the benefits of exercise training in sarcoidosis are scarce.

Scope and aims of the study

The aims of the studies presented in this thesis were to assess the prevalence of muscle weakness and exercise intolerance in sarcoidosis and the usefulness of exercise and/or muscle strength testing in the management of sarcoidosis. Additionally, the predictive value of physical functions for fatigue and QoL were assessed. And finally, the impact of physical training on physical functions and QoL were studied. The studies included patients with sarcoidosis who were referred to a tertiary ild care center in the Netherlands.

Chapter 2 provides an overview of the current literature regarding prevalence, assessment and treatment of muscle weakness and exercise intolerance in sarcoidosis and the association between these physical parameters and fatigue, dyspnea and QoL.
Chapter 3 presents a case-control study performed between November 2008 and September 2009, which reported on the prevalence of exercise intolerance, muscle weakness and fatigue measured with the six-minute walk test, microFET, Biodex System 3 pro and Jamar dynamometer, maximal inspiratory mouth pressures and the FAS in 124 symptomatic Dutch sarcoidosis patients and 62 healthy controls. Also the predictive value of exercise capacity, muscle strength and other clinical characteristics for fatigue was evaluated. **Chapter 4** describes the changes in the prevalence of exercise intolerance, muscle weakness, and fatigue in 90 sarcoidosis patients of the 2008/9 study (chapter 3) and the changes in these parameters in individual patients during a 2-year follow-up study. **Chapter 5** evaluates the additional value of cardiopulmonary exercise testing, performing a symptom-limited incremental exercise test with blood gas analysis on a bicycle ergometer, compared to the measurement of the diffusing capacity of the lung for carbon monoxide (DLCO) in detecting pulmonary gas exchange impairment in 160 sarcoidosis patients with unexplained disabling symptoms. Secondly, the predictive value of physical testing and clinical characteristics for impaired gas exchange was reported. **Chapter 6** assesses the associations between

QoL measured with the WHOQOL-BREF and both physical functions (six-minute walking distance, peripheral and maximal inspiratory muscle strength) and clinical characteristics in 88 symptomatic Dutch sarcoidosis patients and evaluates whether these associations change over a 2-year period. **Chapter 7** shows the impact of a 13-week physical training program (including peripheral muscle and endurance training) for one hour, thrice a week, on fatigue, physical functions and QoL in 18 fatigued sarcoidosis patients and/or patients with exercise intolerance. Finally, **chapter 8** provides a summary of the findings presented in this thesis and a general discussion. Additionally, the implications of the study outcomes for clinical practice are argued and recommendations for future research are briefly discussed.

References

1. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 1999;160:736-755.
2. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. *Lancet* 2014; 383:1155-1167.
3. Morgenthau AS, Iannuzzi MC. Recent advances in sarcoidosis. *Chest* 2011;139:174-182.
4. Baughman RP, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. *Am J Respir Crit Care Med* 2011;183:573-581.
5. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA* 2011;305:391-399.
6. DeRemee RA. The roentgenographic staging of sarcoidosis. Historic and contemporary perspectives. *Chest* 1983;83:128-133.
7. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H, Jr., Bresnitz EA, DePalo L, Hunninghake G, Iannuzzi MC, Johns CJ, McLennan G, Moller DR, Newman LS, Rabin DL, Rose C, Rybicki B, Weinberger SE, Terrin ML, Knatterud GL, Cherniak R, Case Control Etiologic Study of Sarcoidosis research group. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001;164:1885-1889.
8. Rybicki BA, Major M, Popovich J, Jr., Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol* 1997;145:234-241.
9. Drent M. Sarcoïdose: stand van zaken. FarmacotherapieOnline. 2012:1-25. www.farmacotherapie.org.
10. Pietinalho A, Hiraga Y, Hosoda Y, Lofroos AB, Yamaguchi M, Selroos O. The frequency of sarcoidosis in Finland and Hokkaido, Japan. A comparative epidemiological study. *Sarcoidosis* 1995;12:61-67.
11. Izbicki G, Chavko R, Banauch GI, Weiden MD, Berger KI, Aldrich TK, Hall C, Kelly KJ, Prezant DJ. World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers. *Chest* 2007;131:1414-1423.
12. Checchi L, Nucci MC, Gatti AM, Mattia D, Violante FS. Sarcoidosis in a dental surgeon: a case report. *J Med Case Rep* 2010;4:259.
13. Sheu J, Saavedra AP, Mostaghimi A. Rapid response of tattoo-associated cutaneous sarcoidosis to minocycline: case report and review of the literature. *Dermatol Online J* 2014;20.
14. Baughman RP, Lower EE, Gibson K. Pulmonary manifestations of sarcoidosis. *Presse Med* 2012;41: e289-302.
15. Valeyre D, Nunes H, Bernaudin JF. Advanced pulmonary sarcoidosis. *Curr Opin Pulm Med* 2014;20: 488-495.
16. Fayad F, Liote F, Berenbaum F, Orcel P, Bardin T. Muscle involvement in sarcoidosis: a retrospective and followup studies. *J Rheumatol* 2006;33:98-103.
17. Mostard RL, Voo S, Van Kroonenburgh MJ, Verschakelen JA, Wijnen PA, Nelemans PJ, Erckens RJ, Drent M. Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis. *Respir Med* 2011;105:1917-1924.
18. Cremers JP, Van Kroonenburgh MJ, Mostard RL, Voo SA, Wijnen PA, Koek GH, Drent M. Extent of disease activity assessed by 18F-FDG PET/CT in a Dutch sarcoidosis population. *Sarcoidosis Vasc Diffuse Lung Dis* 2014;31:37-45.
19. Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-alpha treatment. *Respiration* 2010;80:212-219.
20. Elfferich MD, De Vries J, Drent M. Type D or 'distressed' personality in sarcoidosis and idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2011;28:65-71.
21. Chang B, Steimel J, Moller DR, Baughman RP, Judson MA, Yeager H, Jr., Teirstein AS, Rossman MD, Rand CS. Depression in sarcoidosis. *Am J Respir Crit Care Med* 2001;163:329-334.
22. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. *Eur Respir J* 2012;40:255-263.
23. De Kleijn WP, De Vries J, Lower EE, Elfferich MD, Baughman RP, Drent M. Fatigue in sarcoidosis: a systematic review. *Curr Opin Pulm Med* 2009;15:499-506.
24. Wirnsberger RM, De Vries J, Wouters EF, Drent M. Clinical presentation of sarcoidosis in the Netherlands an epidemiological study. *Neth J Med* 1998;53:53-60.

25. Spruit MA, Thomeer MJ, Gosselink R, Troosters T, Kasran A, Debrock AJ, Demedts MG, Decramer M. Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. *Thorax* 2005;60:32-38.
26. Alhamad EH. The six-minute walk test in patients with pulmonary sarcoidosis. *Ann Thorac Med* 2009; 4:60-64.
27. Wilsher ML. Psychological stress in sarcoidosis. *Curr Opin Pulm Med* 2012;18:524-527.
28. Wirnsberger RM, Drent M, Hekelaar N, Breteler MH, Drent S, Wouters EF, Dekhuijzen PN. Relationship between respiratory muscle function and quality of life in sarcoidosis. *Eur Respir J* 1997;10:1450-1455.
29. Cremers JP, Drent M, Elfferich MD, Nelemans PJ, Wijnen PA, Witteman BJ, Schols AM. Body composition profiling in a Dutch sarcoidosis population. *Sarcoidosis Vasc Diffuse Lung Dis* 2013;30: 289-299.
30. Spruit MA, Wouters EFM, Gosselink R. Rehabilitation programmes in sarcoidosis: a multidisciplinary approach. *Eur Respir J* 2005;32:316-326.
31. Bourbonnais JM, Malaisamy S, Dalal BD, Samarakoon PC, Parikh SR, Samavati L. Distance saturation product predicts health-related quality of life among sarcoidosis patients. *Health Qual Life Outcomes* 2012;10:67.
32. Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. *Chest* 2007;132:207-213.
33. Drent M, Wirnsberger RM, De Vries J, Van Dieijen-Visser MP, Wouters EF, Schols AM. Association of fatigue with an acute phase response in sarcoidosis. *Eur Respir J* 1999;13:718-722.
34. Verbraecken J, Hoitsma E, Van der Grinten CP, Cobben NA, Wouters EF, Drent M. Sleep disturbances associated with periodic leg movements in chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;21:137-146.
35. Goracci A, Fagiolini A, Martinucci M, Calossi S, Rossi S, Santomauro T, Mazzi A, Penza F, Fossi A, Bargagli E, Pieroni MG, Rottoli P, Castrogiovanni P. Quality of life, anxiety and depression in sarcoidosis. *Gen Hosp Psychiatry* 2008;30:441-445.
36. Hoitsma E, Drent M, Verstraete E, Faber CG, Troost J, Spaans F, Reulen JP. Abnormal warm and cold sensation thresholds suggestive of small-fibre neuropathy in sarcoidosis. *Clin Neurophysiol* 2003;114:2326-2333.
37. Hoitsma E, Marziniak M, Faber CG, Reulen JP, Sommer C, De Baets M, Drent M. Small fibre neuropathy in sarcoidosis. *Lancet* 2002;359:2085-2086.
38. Pereira CA, Dornfeld MC, Baughman R, Judson MA. Clinical phenotypes in sarcoidosis. *Curr Opin Pulm Med* 2014;20:496-502.
39. Baughman RP, Lower EE. Who dies from sarcoidosis and why? *Am J Respir Crit Care Med* 2011;183: 1446-1447.
40. Korenromp IH, Laar MA. Health-related quality of life in sarcoidosis. *Curr Opin Pulm Med* 2014;20: 503-507.
41. Michielsen HJ, Peros-Golubicic T, Drent M, De Vries J. Relationship between symptoms and quality of life in a sarcoidosis population. *Respiration* 2007;74:401-405.
42. De Vries J, Rothkrantz-Kos S, Van Dieijen-Visser MP, Drent M. The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;21:127-136.
43. Wirnsberger RM, De Vries J, Breteler MH, Van Heck GL, Wouters EF, Drent M. Evaluation of quality of life in sarcoidosis patients. *Respir Med* 1998;92:750-756.
44. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WD, Pitta F, Sewell L, Raskin J, Bourbeau J, Crouch R, Franssen FM, Casaburi R, Vercoulen JH, Vogiatzis I, Gosselink R, Clini EM, Effing TW, Maltais F, Van der Palen J, Troosters T, Janssen DJ, Collins E, Garcia-Aymerich J, Brooks D, Fahy BF, Puhan MA, Hoogendoorn M, Garrod R, Schols AM, Carlin B, Benzo R, Meek P, Morgan M, Rutten-van Molken MP, Ries AL, Make B, Goldstein RS, Dowson CA, Brozek JL, Donner CF, Wouters EF. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013;188:e13-64.
45. Kabitz HJ, Lang F, Walterspacher S, Sorichter S, Muller-Quernheim J, Windisch W. Impact of impaired inspiratory muscle strength on dyspnea and walking capacity in sarcoidosis. *Chest* 2006;130:1496-1502.
46. Miller A, Brown LK, Sloane MF, Bhuptani A, Teirstein AS. Cardiorespiratory responses to incremental exercise in sarcoidosis patients with normal spirometry. *Chest* 1995;107:323-329.

47. Drouin JM, Valovich-mcLeod TC, Shultz SJ, Gansneder BM, Perrin DH. Reliability and validity of the Biodex system 3 pro isokinetic dynamometer velocity, torque and position measurements. *Eur J Appl Physiol* 2004;91:22-29.
48. Werle S, Goldhahn J, Drerup S, Simmen BR, Sprott H, Herren DB. Age- and gender-specific normative data of grip and pinch strength in a healthy adult Swiss population. *J Hand Surg Eur Vol* 2009;34:76-84.
49. Bohannon RW. Make tests and break tests of elbow flexor muscle strength. *Phys Ther* 1988;68:193-194.
50. Holland A, Hill C. Physical training for interstitial lung disease. *Cochrane Database Syst Rev* 2008: CD006322.
51. Huppmann P, Sczepanski B, Boensch M, Winterkamp S, Schonheit-Kenn U, Neurohr C, Behr J, Kenn K. Effects of in-patient pulmonary rehabilitation in patients with interstitial lung disease. *Eur Respir J* 2013;42:444-453.